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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,750	03/20/2002	Nobuhiko Nakashima	3190-015	8810

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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,750	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9,12-25 and 27-31* is/are pending in the application.

4a) Of the above claim(s) *1-4,12,14,18,19,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,13,15-17,20-24,27,30 and 31* is/are rejected.

7)☒ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-4, 9, 12-25 and 27-31 are pending.

Applicants' amendment filed on October 7, 2005 is acknowledged. Applicants' response has been fully considered. Claims 16, 20, 21, 24, 25 and 30 have been amended, and claim 26 has been cancelled. Claims 1-4, 12, 14, 18, 19, 28 and 29 are non-elected inventions and withdrawn from consideration. Thus, claims 9, 13, 15-17, 20-25, 27, 30 and 31 are examined.

Sequence Listing

2. A paper copy of sequence listing amended to include original sequence listing (i.e., SEQ ID NOs:1-7, the IGR-IRES regions of various CrP-like viruses; filed March 20, 2002) and additional seven sequences shown in Figs. 1, 2 and 4 (the sequence of SEQ ID NO:1-6 or 7 plus 12 additional bases at the 3' end) filed October 7, 2005 is acknowledged, and CRF has been entered.

Withdrawn Objection

3. The previous objection to the disclosure, regarding the description of Figs. 1, 2 and 4, is withdrawn in view of applicant's amendment to the specification, and applicant's response at page 15 of the amendment filed October 7, 2005.

Withdrawn Claim Rejections - 35 USC § 112

4. The previous rejection of claims 13, 15, 21, 25, 26, 30 and 31 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's cancellation of the claims, applicant's

amendment of the claims, and applicant's response at pages 19-20 of in the amendment filed October 7, 2005.

Withdrawn Claim Rejections - 35 USC § 102

5. Previous rejection of claim 26 under 35 U.S.C. 102(b) as being anticipated by Sasaki *et al.* (J. Virology, 73, 1219-1226 (1999)) is withdrawn in view of applicant's cancellation of the claims in the amendment filed October 7, 2005.

6. The previous rejection of claims 9, 13, 15, 16, 20-24, 26, 30 and 31 under 35 U.S.C. under 35 U.S.C. 102(a) as being anticipated by Sasaki *et al.* (PNAS 97, No. 4, 1512-1515 (February 2000)), is withdrawn in view of applicant's cancellation of the claims, applicant's amendment of the claims, and applicant's response at pages 19-20 of the amendment filed October 7, 2005.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Previous rejection of claims 9, 13, 15-17, 20, 21, 24, 27, 30 and 31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Claims 9, 13, 15-17, 20, 21, 24, 27, 30 and 31 are directed to a method of synthesizing a heterologous polypeptide or a method of initiating synthesis of arbitrary heterologous polypeptide *in vitro*, the method comprising utilizing a polynucleotide that promotes translation activity and has an RNA higher-order structure including PK (pseudoknot) I, II and III structures, wherein the polynucleotide encoding the heterologous polypeptide is immediately downstream from the PKI structure of the polynucleotide that promotes translation activity, and wherein the RNA higher-order structure may comprise a base sequence of SEQ ID NO:1-6 or 7, a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been modified and has a function for promoting a translation activity. While the specification discloses an RNA higher-order structure having a function of promoting translation activity contains a base sequence of SEQ ID NO:1-6 or 7 (pages 6-7); the RNA higher-order structure of SEQ ID NO:1 containing three pseudoknot structures (PK I, II and III) contributes to the initiation and acceleration of translation of a protein (e.g., luciferase) *in vitro* and a specific mutation of PK I in the PSIV-IRES permits translation of a GFP gene, where *in vitro* translation was carried out using a rabbit reticulocyte lysate (Example 1; Figs. 7 and 8); and utilizing a mutated PSIV-IRES permitted translating a heterologous protein that begins with an arbitrary amino acid in cell-free system using a wheat germ extract (Example 2, Fig. 9), it does not describe a genus of variants for an RNA higher-order structure having PK I, II and III structures and a function for promoting translation activity, where the polynucleotide sequence of the RNA higher-order structure is not defined, or the polynucleotide sequence, which is related to SEQ ID NO:1-7, is not identified. For example, the

specification does not identify the portion of the polynucleotide sequence identical to the base sequence of SEQ ID NO:1-7 in the sequence having at least 50% homology to the base sequence, which nucleotides in the base sequence are modified (i.e., including deletion, substitution, addition or insertion) and remain functional, or, which sequence hybridizing to the base sequence under stringent condition or which complementary sequence of a base sequence variant is functional; nor demonstrates any of these polynucleotide variants has translation activity. Without guidance on structure to function/activity relationship for variants of RNA higher-order structure or variants of SEQ ID NO:1-7, one skilled in the art would not know which nucleotides in the RNA higher-order structure or SEQ ID NO:1-7 are essential for its translation activity, and how to identify a functional polynucleotde among numerous polynucleotides. The lack of description of the structure to function/activity relationship for variants of an higher-order RNA structure or SEQ ID NO:1-7 and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Argument

Applicants indicate the present specification contains a thorough explanation of what is meant by an RNA higher-order structure including PK (pseudoknot) I, II, and III structures, particularly in Example 1 at pages 14 - 15 and Figures 5 - 6. The genus of polynucleotides that contain the RNA higher-order structures including PK (pseudoknot) I, II, and III structures is thoroughly described on pages 4-8. Further, the guidelines provided by the USPTO in the M.P.E.P, Section 2163 state that the written description requirement may be satisfied through a

sufficient description of a representative number of species or by disclosure of relevant, identifying characteristics, such as structure or other physical or chemical properties. The present invention provides both: a thorough description of the higher order structure including PK I, II, and III structures and seven examples (SEQ ID NO: 1-7) of polynucleotides containing this structure, with a thorough illustration in Figures 4 - 6 of how the higher order structure is formed by base pairing in each of SEQ ID NO:1-7. Regarding the comments by Examiners that the specification does not teach how to identify a functional polynucleotide among sequences related to SEQ ID NO: 1-7, the specification clearly teaches, for instance, at pages 14 -15 that a polynucleotide that has the base pair and stem loop formation for forming the higher order structure for promoting translation can be determined with an RNA secondary structure-predicting program such as MFOLD, and the formation of a higher order structure can be readily identified from structures that have the correct stem loop formation in their secondary structure by determining base pairing as illustrated in Figures 5 and 6. Therefore, identifying functional polynucleotides according to the present invention is well within the skill of persons skilled in the art combined with the teachings of the present specification. Moreover, the Examiner has not presented any specific reason for including claim 24 in this rejection. Claim 24 is directed to the method of the present invention wherein the RNA higher-order structure comprises a base sequence of the sequences of SEQ ID NOs: 1-7, except that the base sequence contains an alteration in one or more combinations of base pairs that make up PKI so that polynucleotide that promotes translation activity is able to initiate translation activity of a heterologous protein or heterologous peptide without an AUG translation initiation codon (see pages 13-14 of the

specification). Thus, the specification provides a written description of the claimed invention (pages 16-19 of the response).

Applicants' response has been considered, however, the argument is not persuasive because the specification merely describes specific higher-order RNA structures with a defined base sequence of SEQ ID NO:1-7 (Example 1, Figs. 15 and 16; pages 5-6) and a specific mutation in the in the PK I of PSIV-IRES (Fig. 7), and provides a general description regarding sequence homology, mutation, complementary sequence or hybridization on the base sequence of SEQ ID NO:1-7 (pages 7-8), it does not provide sufficient teachings on the identities of the functional polynucleotide variants for higher-order RNA structures with no defined sequences, or for polynucleotides related to variants of SEQ ID NO:1-7 such as sequences having at least 50% homology to SEQ ID NO:1-7 and modified sequence of SEQ ID NO:1-7. Regarding using an RNA secondary structure-predicting program such as MFOLD to identify the formation of a higher order structure, the specification also indicates the method does not permit detecting any conservation concerning the complementary sequence playing an important role in the function of IRES, thus, a mutation introduction experiment has to be used to investigate the function of RNA higher-order structure (page 14). Thus, a polynucleotide without a defined sequence cannot be identified to have an RNA higher-order structure, and even a polynucleotide variant of SEQ ID NO:1-7 can be identified to have higher-order structure, the function of the polynucleotide variant of SEQ ID NO:1-7 can only be verified with further experimentation. Therefore, without establishing the correlation of the structure to function/activity for variants of higher-order RNA structures or SEQ ID NO:1-7, the functional polynucleotide variant of higher-order RNA structures or SEQ ID NO:1-7 cannot be readily identified. Regarding claim 24, since

the specification only discloses a specific mutation in PKI of SEQ ID NO:1 (pages 13-14), it does not discloses an alteration (i.e., deletion, substitution, addition or insertion) in one or more combinations of base pairs that make up PKI of the base sequence so that polynucleotide that promotes translation activity. Therefore, applicants have failed to sufficiently describe the claimed invention that a skilled artisan would not recognize applicants were in possession of the claimed invention.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because the claim, which recites at least PK I, II and III structures are maintained in the RNA higher-order structure, does not further limit claim 21, which depends from claim 20, and claim 20 recites the polynucleotide has an RNA higher-order structure including PK I, II and III structures.

Maintained Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Previous rejection of claims 9, 13, 15, 16 and 20-23 under 35 U.S.C. 102(b) as being anticipated by Sasaki *et al.* (J. Virology, 73, 1219-1226 (1999)) is maintained. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Sasaki *et al* teach AUG-unrelated translation initiation is mediated by the internal ribosome entry site (IRES) of an insect picorna-like virus (i.e., *Plautia stali* intestine virus (PSIV)) *in vitro*, where the positive-strand RNA genome of the virus contains two non-overlapping open reading frames (ORFs), and the capsid protein gene is located in the 3'-proximal ORF and lacks an AUG initiation codon (Fig. 1); the capsid protein gene was translated cap independently in the presence of the upstream cistron, indicating that the capsid protein is translated by internal ribosome entry; (pages 1220-1221; Figs 2 and 3). The reference also teaches a LUC (luciferase) gene was used as the second cistron, and in the CAT-IRES-LUC series of constructs, LUC genes without an AUG initiation codon was ligated to the PSIV sequences (Fig. 5; claims 9, 15, 16), and the LUC gene was efficiently translated when fused down stream of nt 6201 (pCAT-$IRES_{6201}$-LUC) and nt 6264 (pCAT-$IRES_{6264}$-LUC) in vitro (pages 1221-1222; Figs. 5 and 7; claim 20), where the 3' boundary of the IRES is located between nt 6196 and 6201, which indicates the IRES extends into the capsid-coding region (page 1222, left column, lines 1-5) and the $IRES_{6201}$ contains SEQ ID NO:1 (nt 6005-6192, 188 nucleotides; claims 13, 21, 22 and 23). Although the reference does not specifically indicate the $IRES_{6201}$ of PSIV has an RNA higher-order structure (PK I, II or III), the $IRES_{6201}$ sequence contains SEQ ID NO:1 and has the function of promoting translation activity, thus it would be expected that the IRES sequence has at least PK I, II or III structure, thus the reference anticipates the claimed invention.

Response to Argument

Applicants indicate Sasaki *et al.* confirms only the translation of a virus coat protein and luciferase genes as a fusion protein, that is, a protein that contains at least some of both the native virus coat protein and luciferase. While claims 20 and 30 of instant application, as amended, clarify that in the synthesis of a heterologous protein or polypeptide, the polynucleotide encoding the heterologous protein or heterologous polypeptide is immediately downstream from the PKI structure of the polynucleotide that promotes translation activity. As described in the sequence listing, a previous error in the sequence listing has been corrected so that SEQ ID NO: 1-7 do not include the virus coat protein encoding region of the sequences illustrated in Figs. 1, 2, and 4. Therefore, in the method of the present invention, there is no polynucleotide encoding a virus coat protein between the polynucleotide that promotes translation activity and the polynucleotide encoding the heterologous protein. This allows for the heterologous protein alone to be synthesized instead of a fusion protein that contains a portion of a virus coat protein along with the heterologous protein. In fact, Sasaki *et al.* (J. Virology) teaches away from the present invention by providing data that suggests that it is not possible to synthesize a protein using IRES unless a portion of the virus coat protein is included in the synthesis (see lanes 2 and 3 in Fig. 5). For these reasons, the rejection should be withdrawn (pages 20-22 of the response).

Applicants' response has been considered, however, the argument is not persuasive because the reference teaches in CAT-IRES-LUC series of constructs, LUC genes without an AUG initiation codon was ligated to the PSIV sequences (Fig. 5), and the LUC gene was efficiently translated when fused down stream of nt 6201 (pCAT-IRES$_{6201}$-LUC, Fig. 5 lane 4) in vitro, where the 3' boundary of the IRES is located between nt 6196 and 6201, which indicates

the IRES extends into the capsid-coding region (page 1222, left column, lines 1-5), and the $IRES_{6201}$ contains the same SEQ ID NO:1 as the claimed invention. Since the claim recites the polynucleotide encoding the heterologous protein is immediately downstream from PKI structure without indicating the nucleotide positions of the PKI structure, and the reference teaches the construct of pCAT-$IRES_{6201}$-LUC, where the 3' boundary of the IRES is located between nt 6196 and 6201, and the $IRES_{6201}$ of PSIV comprises SEQ ID NO:1, which has a function of promoting translation activity, thus, the polynucleotide of pCAT-$IRES_{6201}$-LUC meets the limitation for the claimed method.

Claim Objection

10. Claim 25 is objected to because the claim is dependent from a rejected claim, claim 20.

Conclusion

11. Claims 9, 13, 15-17, 20-24, 27, 30 and 31 are rejected; and claim 25 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
December 19, 2005